Risk of infections of biological and targeted drugs in patients with spondyloarthritis: meta-analysis of randomized clinical trials

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Abstract

Background: Concerns exist regarding the risk of infections in patients with spondyloarthritis (SpA) treated with biologics. We assessed the risk of infections of biological and targeted drugs in patients with SpA by performing a meta-analysis based on randomized controlled trials (RCTs).

Methods: A systematic literature search was conducted in PubMed, Embase, Web of Science, the Cochrane Library, and China Biology Medicine Disc for RCTs evaluating the risk of infections of biological therapy in patients with SpA from inception through August 9, 2021. We calculated a pooled Peto odds ratio (OR) for infections in biologics-treated patients *vs.* placebo patients. The risk of bias on the included RCTs was assessed by using the Cochrane Risk of Bias Tool.

Results: In total, 62 studies were included in this meta-analysis. Overall, the risk of infection (Peto OR: 1.16, 95% confidence interval [CI]: 1.07–1.26, $P < 0.001$), serious infection (Peto OR: 1.65, 95% CI: 1.26–2.17, $P < 0.001$), upper respiratory tract infection (URTI) (Peto OR: 1.17, 95% CI: 1.04–1.32, $P = 0.008$), nasopharyngitis (Peto OR: 1.25, 95% CI: 1.10–1.42, $P < 0.001$), and *Candida* infection (Peto OR: 2.64, 95% CI: 1.48–4.71, $P = 0.001$) were increased in SpA patients treated with biologics compared with placebo. Sensitivity analysis based on biologics classes was conducted, and results demonstrated that compared with placebo, there was a higher risk of infection for tumor necrosis factor (TNF)-α inhibitors (Peto OR: 1.38, 95% CI: 1.13–1.68, $P = 0.001$) and interleukin (IL)-17 inhibitors (Peto OR: 1.55, 95% CI: 1.08–2.22, $P = 0.018$) in axial SpA, and for Janus kinase inhibitors in peripheral SpA (Peto OR: 1.39, 95% CI: 1.14–1.69, $P = 0.001$); higher risk of serious infection for IL-17 inhibitors in peripheral SpA (Peto OR: 3.46, 95% CI: 1.26–9.55, $P = 0.016$) and axial SpA (Peto OR: 2.01, 95% CI: 1.38–2.91, $P < 0.001$); higher risk of URTI for TNF-α inhibitors in axial SpA (Peto OR: 1.37, 95% CI: 1.05–1.78, $P = 0.019$), and for apremilast in peripheral SpA (Peto OR: 1.60, 95% CI: 1.08–2.36, $P = 0.018$); higher risk of nasopharyngitis for TNF-α inhibitors in axial SpA (Peto OR: 1.41, 95% CI: 1.05–1.90, $P = 0.022$) and peripheral SpA (Peto OR: 1.49, 95% CI: 1.09–2.05, $P = 0.013$), and for IL-17 inhibitors in axial SpA (Peto OR: 1.35, 95% CI: 1.01–1.82, $P = 0.044$); higher risk of herpes zoster for Janus kinase inhibitors in peripheral SpA (Peto OR: 2.18, 95% CI: 1.03–4.62, $P = 0.043$); higher risk of *Candida* infection for IL-17 inhibitors in peripheral SpA (Peto OR: 2.52, 95% CI: 1.31–4.84, $P = 0.006$).

Conclusions: This meta-analysis shows that biological therapy in patients with SpA may increase the risk of infections, including serious infections, URTI, nasopharyngitis, and *Candida* infection, which should be paid attention to in our clinical practice.

Keywords: Spondyloarthritis; Biological therapy; Infection; Herpes zoster; Meta-analysis

Introduction

Spondyloarthritis (SpA) is a series of chronic inflammatory conditions that have a range of manifestations, including predominantly axial SpA (radiographic axial SpA [axSpA] and non-radiographic axial SpA) and peripheral SpA (enteropathic arthritis, reactive arthritis, and psoriatic arthritis).[1] People with predominantly axSpA may have additional peripheral symptoms, and *vice versa*. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), or a combination of both, can usually ameliorate disease activity and retard joint damage, thereby improving the quality of life of patients with SpA. However, in a sizeable proportion of patients with SpA, NSAIDs, or csDMARDs fail or are not tolerated. For these patients not responding to NSAIDs or csDMARDs, biologics or small molecular targeted drugs can provide clinically important improvement via targeting specific inflammatory mediators in inflammatory pathways, alleviating inflammation, and thus better controlling symptoms and structural destruction.[2,3]

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Concerns have been raised about the safety of biologics or small molecular targeted drugs, due to their immunosuppressive effects that may contribute to an increased risk of infections in these patients. In turn, the infections may further aggravate the symptoms of patients with SpA, which is the most contradiction in making biologics treatment decisions. Therefore, it is very important to make optimal decisions after weighing the benefits and risks of treatments based on the patient's individual conditions and to keep alert to the risk of developing serious infections during the treatments of biologics.

At present, many randomized controlled trials (RCTs) have reported the infections of biologics and small molecular targeted drugs in the treatment of SpA. However, RCTs are inadequate for detecting and quantifying a small number of events, such as viral and fungal infections, serious infections, and opportunistic infections. A meta-analytic approach is considered useful to overcome the inherent limitations of individual RCTs in the assessment of safety outcomes. The main objective of the systematic review is to summarize and contextualize the risk of infections accompanying biologics and small molecular targeted drugs use in RCTs via using meta-analysis.

Methods

We strictly followed the Preferred Reported Items for Systematic Reviews and Meta-analyses guidelines and the recommendations from the Cochrane Collaboration to conduct this systematic review and meta-analysis.[4]

Data sources and searches

An information specialist and experienced medical librarian was invited to conduct a comprehensive literature search. The following electronic bibliographic databases: PubMed, Embase, the Cochrane Library, Web of Science, and the China Biology Medicine disc (CBM), were searched from inception through August 9, 2021. No limits were applied to race, sex, or language, except for human subjects. The details of search strategies for the electronic database were shown in Appendix 1, http://links.lww.com/CM9/A879. Other resources were hand-searched, including websites and bibliographic references from RCTs and systematic reviews of interest, for additional citations not identified through the original search strategy.

Selection of the trials

Study inclusion was assessed by two pairs of independent researchers (Siliang Man and Xiaojian Ji, Yiwen Wang and Chuan Song). Disagreements were discussed and resolved through consensus and, when needed, a third researcher acted as an adjudicator (Lidong Hu) until a consensus was reached.

Eligible trials were required to (1) be RCTs comparing the safety (infections) of the biologics (tumor necrosis factor [TNF]-α inhibitors, interleukin (IL)-17 inhibitors, IL-6 inhibitors, IL-23 inhibitors, small molecule targeted drugs, and so on) against placebo, NSAIDs, or any csDMARD; (2)

include only patients with SpA including axial SpA and peripheral SpA; and (3) have at least one 12-week follow-up.

Data extraction and risk of bias assessment

Two reviewers (Siliang Man and Xiaojian Ji) independently extracted the data of each trial and the other two reviewers (Yiwen Wang and Jiaxin Zhang) checked the extracted results. Disagreements were discussed and solved through consensus, and a third reviewer acted as an adjudicator (Lidong Hu) if necessary. For each selected RCTs, we collected general information (eg, authors' name, publication year, country, and study design), study population (eg, age of patients and gender distribution), and intervention characteristics (details of intervention and control, duration of intervention, and follow-up). Primary outcome data was the number and type of infections.

All included trials were assessed for risk of bias by two reviewers (Siliang Man and Xiaojian Ji) with version 2 of the Cochrane Risk of Bias Assessment Tool.[5] The following domains of individual trials were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases (including carryover, extreme baseline imbalance, and funding). We assessed the risk of bias using the categories of yes (low risk of bias), no (high risk of bias), and unclear (lack of information or uncertainty about potential bias).

Data synthesis and analysis

We identified the number of patients with at least one outcome of interest, based on the analysis of the adverse event in an individual trial. The number of patients with SpA receiving at least one dose of the study drug represented the denominator of our outcome measurement.

Our study protocol required the use of a fixed-effect model for meta-analysis due to its superior performance while pooling the clinical trials with a small number of events, and the results were expressed as Peto odds ratio (OR) and associated 95% confidence interval (CI). We stratified by biologics classes to explore how different biologics classes affect the risk of infections.

Meta-analysis was conducted using the "meta" package on R software (version 3.6.2 x64; The R Foundation for Statistical Computing). P value < 0.05 was considered a significant difference in all tests.

Results

Literature selection and trial characteristics

A total of 13,103 unique citations were identified through electronic bibliographic databases and hand-searching. There were 8925 records that were potentially relevant to our topic in our first selection round, of which 166 were deemed eligible for a full review. Finally, a total of 62 trials met inclusion criteria for this systematic review and meta-analysis. All the included studies were reported in Chinese or English. The details of the study selection process were

shown in Supplementary Figure 1, http://links.lww.com/CM9/A877.

The 62 RCTs containing 19,411 patients with SpA, were published between 2002 and 2021. Among these RCTs, 25 investigated axSpA and 37 investigated peripheral SpA. A majority of RCTs were two-arm clinical trials, with placebo-controlled periods ranging from 12 to 30 weeks (Supplementary Table 1, http://links.lww.com/CM9/A878).

Risk of bias assessments

Ninety percent of studies provided sufficient details of randomization. Although most of the clinical trials declared that they were double-blind, more than half of the trials indicated inadequate methods of allocation concealment. In all studies, the co-interventions and baseline characteristics were similar between the biologics group and control group (placebo, NSAIDs, and csDMARDs) were grouped together. In some patients who previously received TNF-α inhibitors, switching to other biologics (such as IL-17 inhibitors) might introduce a potential risk of bias. In some trials, the method of the imputation of no response, with "advancement penalty," was used to address this potential risk of bias. The risk of bias graph of assessment for all the included RCTs was demonstrated in Figure 1.

Serious infections

Serious infections were reported in 37 of 62 retrieved RCTs. Across these studies, the patients of serious infection with biological treatments and placebo were 236 (2.60%) and 82 (1.59%), respectively. The measurement of inconsistency between the RCTs (I^2) was 15% ($P = 0.22$), which indicated that there was no statistical heterogeneity in these trials. Overall, there was an increased risk of serious infections in patients with SpA using biological and targeted drugs $vs.$ placebo (Peto OR 1.65, 95% CI: 1.26–2.17, $P < 0.001$; Figure 2).

Subgroup analysis of trials was conducted by using biologics classes. The risks of serious infections were

higher than placebo for IL-17 inhibitors in patients with peripheral SpA (Peto OR: 3.46, 95% CI: 1.26–9.55, $P = 0.016$; $I^2 = 0\%$, $P = 0.87$) and axial SpA (Peto OR: 2.01, 95% CI: 1.38–2.91, $P < 0.001$; $I^2 = 0\%$, $P = 0.52$). There was no significant difference between other biologics and placebo in patients with peripheral SpA and axial SpA [Figure 2].

Common infections

Common infections were reported in 34 of 62 retrieved RCTs. Across these studies, the patients of infection with biological treatments and placebo were 2353 (27.55%) and 1208 (24.34%), respectively. Overall, there was an increased risk of infections in individuals with SpA using biological and targeted drugs $vs.$ placebo (Peto OR 1.16, 95% CI: 1.07–1.26, $P < 0.001$), with low heterogeneity ($I^2 = 16\%$, $P = 0.19$) [Figure 3].

The subgroup analysis consisted of these RCTs providing data on different biologics classes. The results demonstrated that compared with placebo, there was a higher risk of infection for TNF-α inhibitors (Peto OR: 1.38, 95% CI: 1.13–1.68, $P = 0.001$; $I^2 = 0\%$, $P = 1.00$) and IL-17 inhibitors (Peto OR: 1.55, 95% CI: 1.08–2.22, $P = 0.018$; $I^2 = 0\%$, $P = 0.90$) in axial SpA, and for Janus kinase (JAK) inhibitors in peripheral SpA (Peto OR: 1.39, 95% CI: 1.14–1.69, $P = 0.001$; $I^2 = 0\%$, $P = 0.91$). There was no significant difference between other biologics and placebo in patients with peripheral SpA and axial SpA [Figure 3].

Upper respiratory tract infection

Upper respiratory tract infection (URTI) was reported in 49 studies. Across these studies, the patients of URTI with biological treatments and placebo were 906 (7.30%) and 472 (6.78%), respectively. Overall, there was an increased risk of URTI in individuals with SpA using biological and targeted drugs $vs.$ placebo (Peto OR 1.17, 95% CI: 1.04–1.32, $P = 0.008$), with low heterogeneity ($I^2 = 5\%$, $P = 0.37$) [Figure 4].
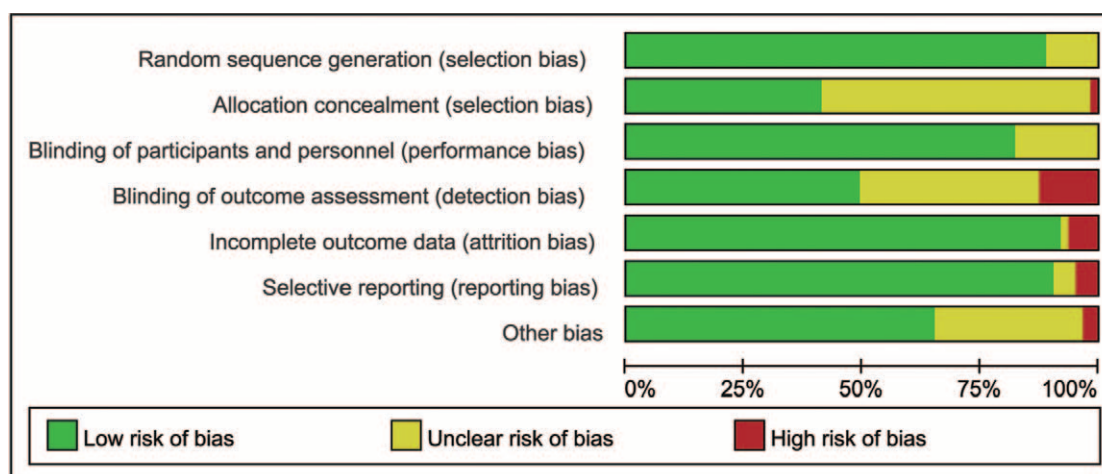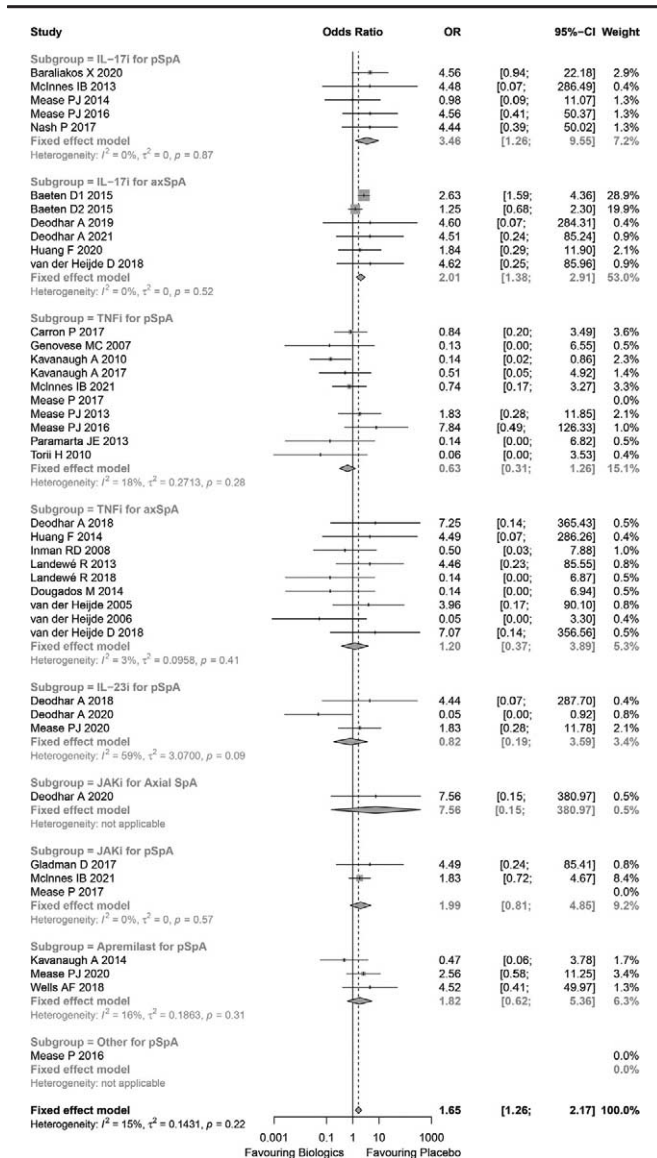

Figure 1: Risk of bias graph.

Figure 2: Forest plot of meta-analyses comparing biologics *vs.* placebo for risk of serious infections. OR: Odds ratio.

Figure 3: Forest plot of meta-analyses comparing biologics *vs.* placebo for risk of common infections. OR: Odds ratio.

The subgroup analysis, based on different biologics classes, demonstrated a higher risk of URTI for TNF-α inhibitors in axial SpA (Peto OR: 1.37, 95% CI: 1.05–1.78, $P = 0.019$; $I^2 = 24\%$, $P = 0.20$) and for apremilast in peripheral SpA (Peto OR: 1.60, 95% CI: 1.08–2.36, $P = 0.018$; $I^2 = 46\%$, $P = 0.10$), compared with placebo. There was no significant difference between other biologics and placebo in patients with peripheral SpA and axial SpA [Figure 4].

Nasopharyngitis

Nasopharyngitis was reported in 40 studies. Across these studies, the patients of nasopharyngitis with biological treatments and placebo were 792 (7.56%) and 356 (6.03%), respectively. Overall, patients with SpA treated with biological and targeted drugs showed an increased risk of nasopharyngitis than placebo (Peto OR 1.25, 95% CI 1.10–1.42, $P < 0.001$), with low heterogeneity ($I^2 = 0\%$, $P = 0.54$) [Figure 5].
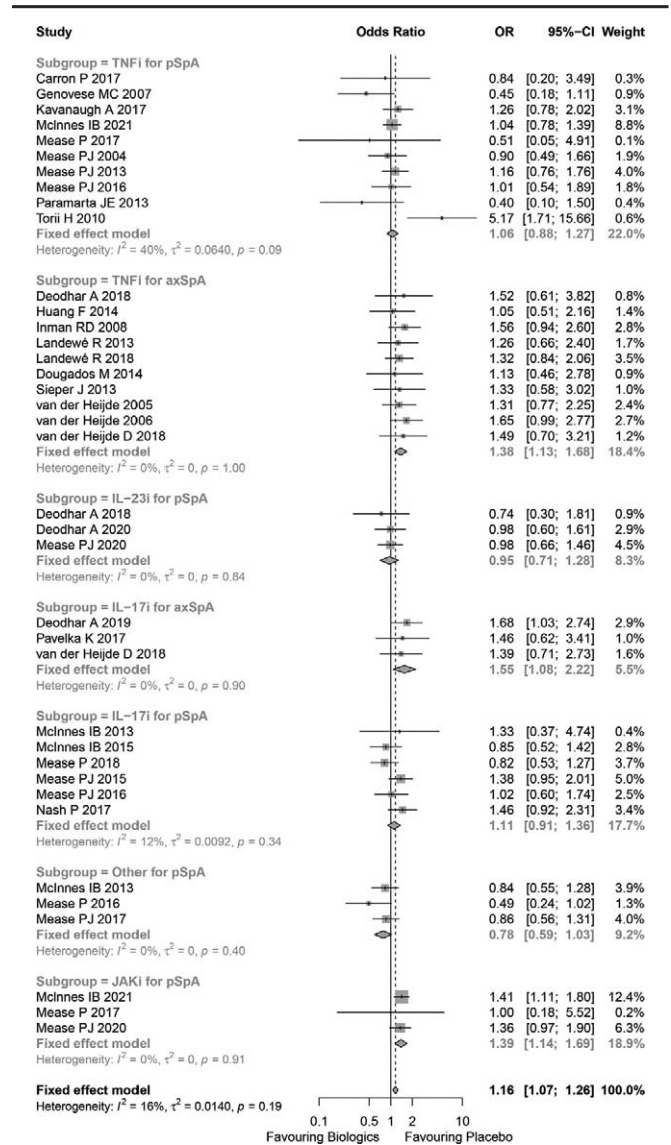
The subgroup analysis, based on different biologics classes, demonstrated a higher risk of nasopharyngitis for TNF-α inhibitors in peripheral SpA (Peto OR: 1.49, 95% CI: 1.09–2.05, $P = 0.013$; $I^2 = 0\%$, $P = 0.73$) and axial SpA (Peto OR: 1.41, 95% CI: 1.05–1.90, $P = 0.022$; $I^2 = 0\%$, $P = 0.88$), and for IL-17 inhibitors in axial SpA (Peto OR: 1.35, 95% CI: 1.01–1.82, $P = 0.044$; $I^2 = 9\%$, $P = 0.36$). There was no significant difference between other biologics and placebo in patients with peripheral SpA and axial SpA [Figure 5].

Candida infection

Candida infection (high-level term) was reported in 14 studies. Overall, patients with SpA treated with biologics showed an increased risk of *Candida* infection than placebo (Peto OR 2.64, 95% CI: 1.48–4.71, $P = 0.001$), with low heterogeneity ($I^2 = 0\%$, $P = 0.81$) [Figure 6]. The subgroup analysis, based on different biologics classes,
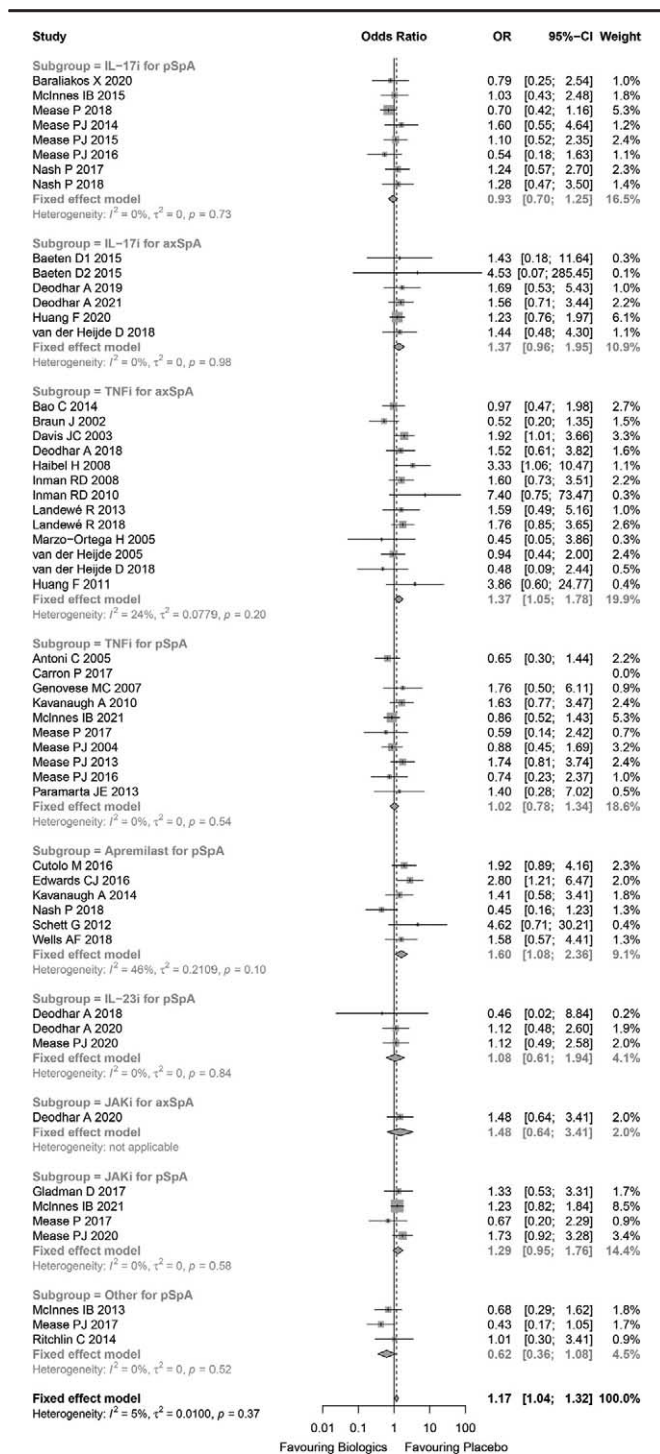
Figure 4: Forest plot of meta-analyses comparing biologics *vs.* placebo for risk of URTI. OR: Odds ratio; URTI: Upper respiratory tract infection.

Figure 5: Forest plot of meta-analyses comparing biologics *vs.* placebo for risk of nasopharyngitis. OR: Odds ratio.

(Peto OR 2.18, 95% CI: 1.03–4.62, $P = 0.043$), with low heterogeneity $(I^2 = 0\%, P = 0.77)$ [Figure 7].

Publication bias

Potential publication bias for serious infection as the primary outcome was assessed by visual inspection of funnel plot for asymmetry and Begg's test. The result showed that the funnel plot was symmetrical and no evidence of publication bias was found [Supplementary Figure 2, http://links.lww.com/CM9/A877]. The same result was also reflected in Begg's test $(z = -0.71, P = 0.477)$.

demonstrated a higher risk of *Candida* infection for IL-17 inhibitors in peripheral SpA (Peto OR: 2.52, 95% CI: 1.31–4.84, $P = 0.006$; $I^2 = 0\%$, $P = 0.64$) [Figure 6].

Herpes zoster

Herpes zoster was reported in eight studies. The results of the meta-analysis showed an increased risk of herpes zoster for JAK inhibitors in peripheral SpA than placebo
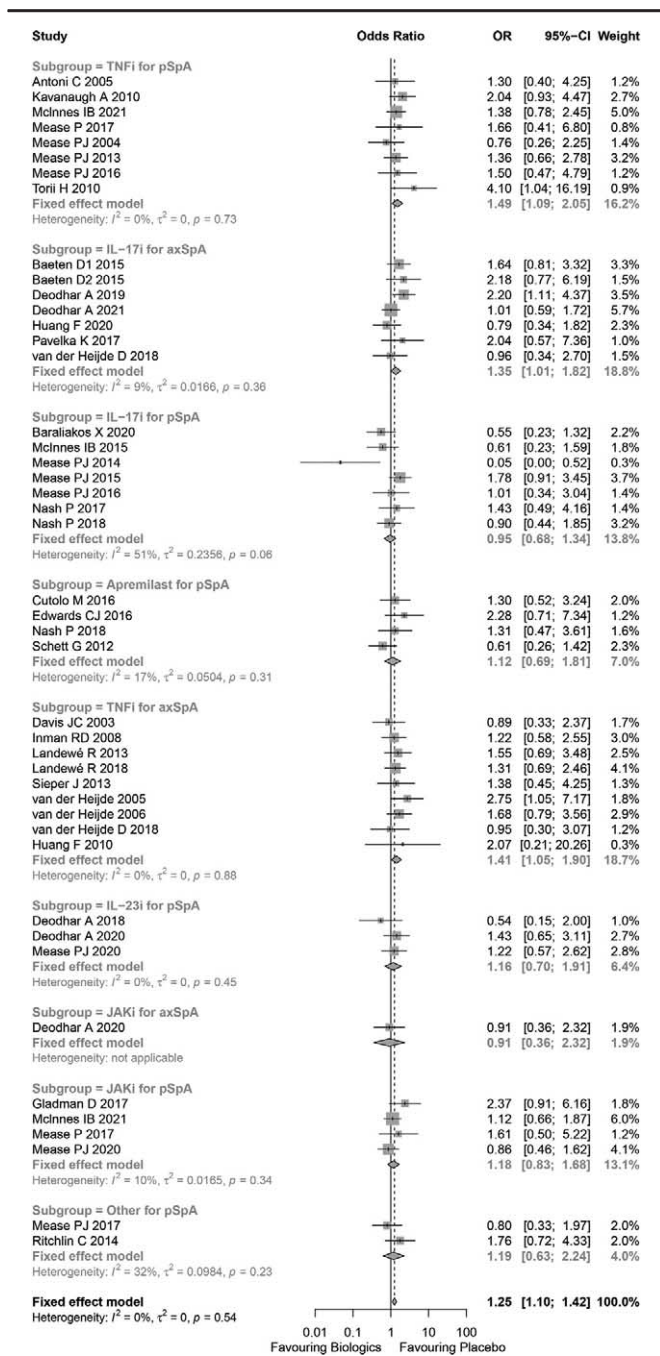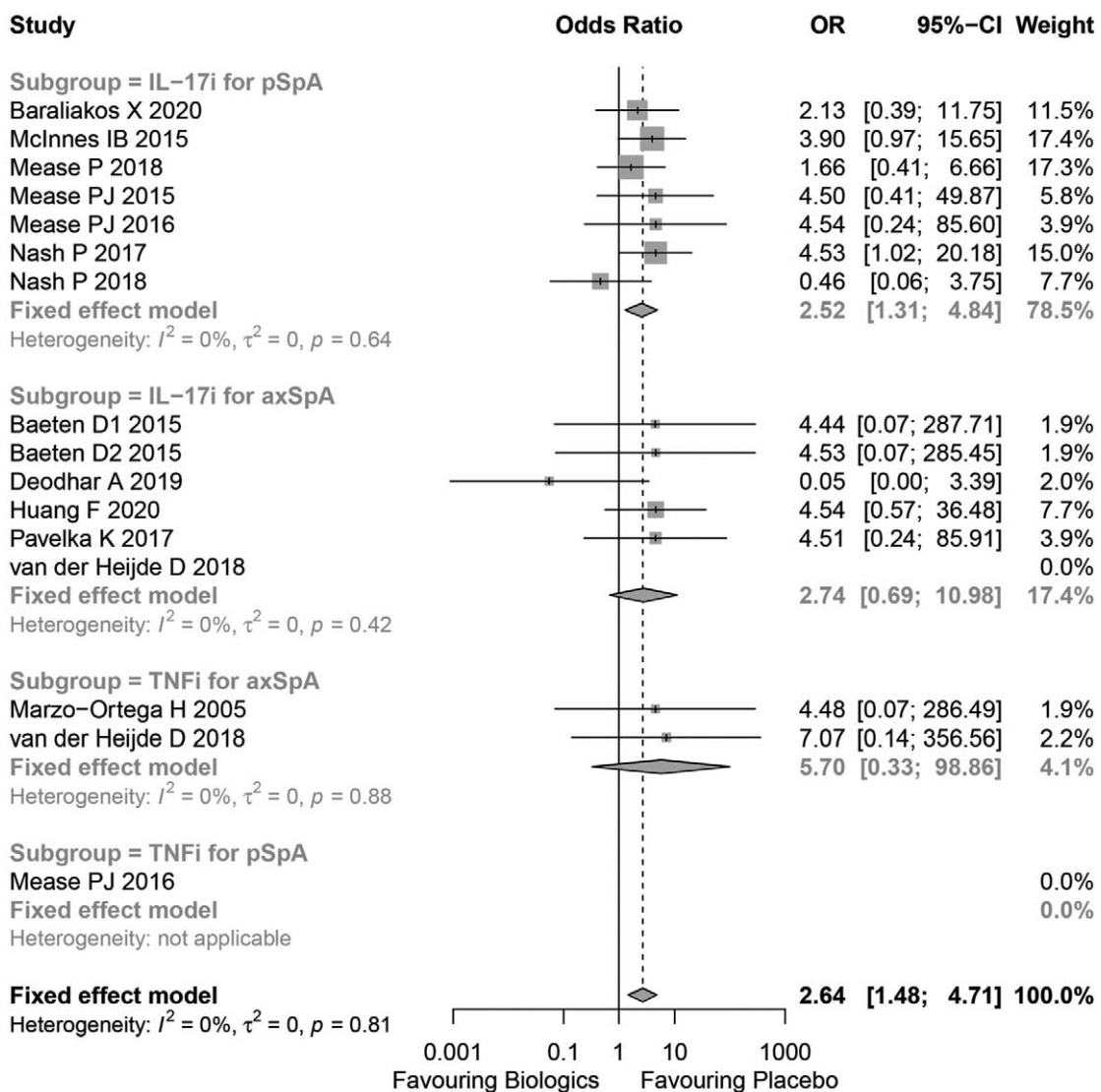
Figure 6: Forest plot of meta-analyses comparing biologics *vs.* placebo for risk of *Candida* infection. OR: Odds ratio.

Discussion

There has been concern regarding a putative increasing risk of infections with either biological or small molecular targeted drugs treatment because of the impacts of these therapies on the immune system. This systematic review and meta-analysis covered 62 published RCTs including 19,411 patients with SpA. The crude pooled results showed that there was an elevated risk of infections, including serious infections, URTI, nasopharyngitis, *Candida* infection, and herpes zoster, in patients with SpA receiving biologics and/or small molecular targeted drugs therapy, compared with placebo.

Stratified according to the treatment with biologics by different types of biological agents in each SpA type, we found that the risk of serious infections was higher for patients with peripheral SpA and axial SpA treated with IL-17 inhibitors during the placebo-controlled periods.

IL-17, as a pro-inflammatory cytokine, plays a vital role in mediating autoimmune inflammatory diseases, but it also plays a very important role in defense against infection caused by extracellular pathogens.[6-8] A study demonstrated a reduced survival and increased bacterial burden in *IL-17A*^{−/−} mice infected with *Klebsiella pneumoniae* and severely impaired neutrophil levels in the lung. This was related to the decrease of CXC chemokines and granulocyte colony-stimulating factor (G-CSF) in bronchoalveolar lavage fluid.[9] Another study showed an independent requirement for IL-23 in pulmonary host defense against infection of *K. pneumoniae,* which was required for IL-17 production.[10] Besides, IL-17 is also important for protection against intracellular bacteria. Studies demonstrated that infections with *Francisella tularensis* and *Chlamydia* required the involvement of IL-17, the former of which was regulated through the induction of IL-12 and interferon-γ mediated by IL-17 in macrophages, linking Th1 and Th17 responses *in vivo*.[11,12]
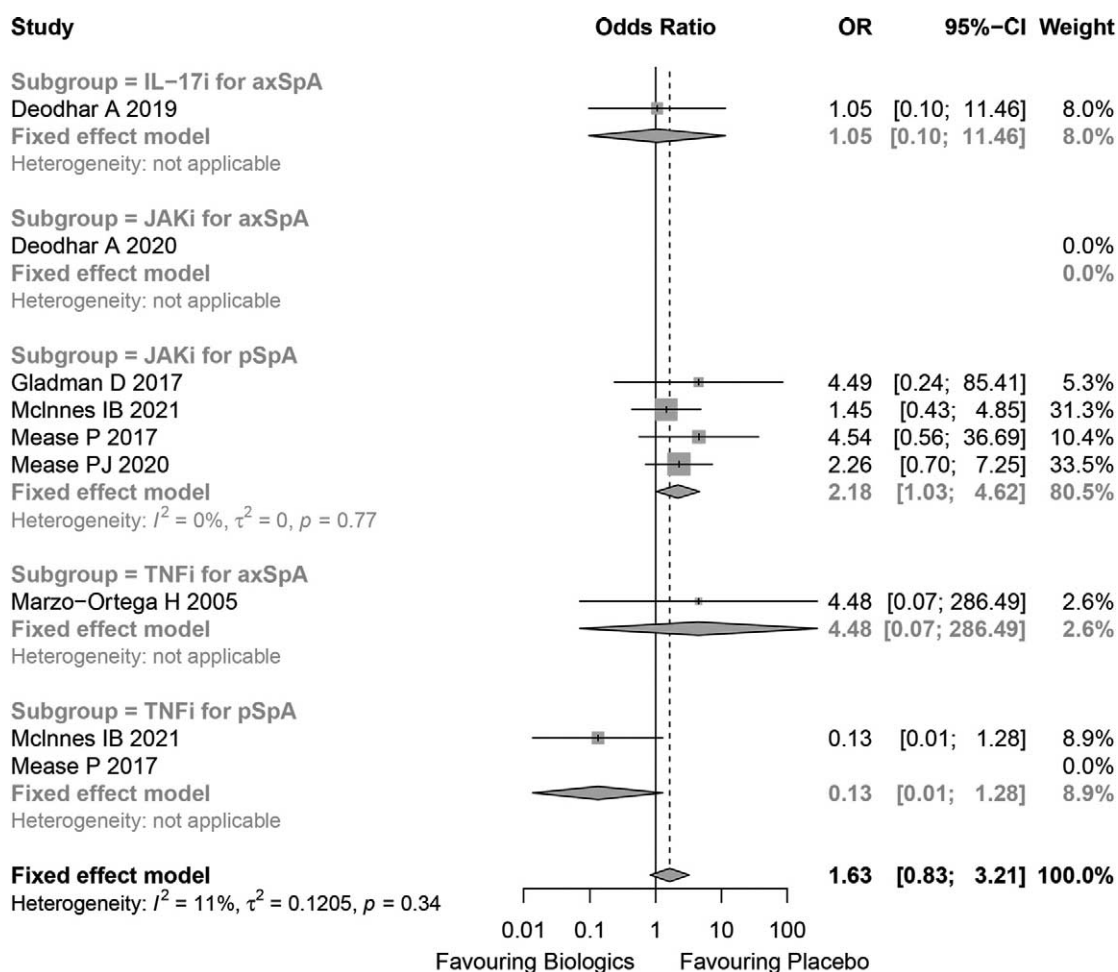
Figure 7: Forest plot of meta-analyses comparing biologics *vs.* placebo for risk of herpes zoster. OR: Odds ratio.

In addition, in our study, we found a higher risk of *Candida* infection for IL-17 inhibitors in peripheral SpA. IL-17 plays an important protective role in the setting of fungal infections. Two mouse models infected with oropharyngeal *Candida* indicated that IL-17 and IL-23 played a very important role in defense against mucosal *C. albicans.* Furthermore, microarray analysis demonstrated that after immunocompetent wild-type mice were infected with *C. albicans,* expression of many classical IL- 17 target genes in the oral mucosa was upregulated, including beta-defensin 3, G-CSF, IL-6, matrix metalloproteinase-8, chemokine CXCL1, and CXCL5.[13] Another study showed that the release of IL-17 upon stimulation with *Candida* in peripheral blood mononuclear cells from the patients with acute *Candida* infection was significantly higher than the healthy control. These indicated the importance of IL-17 in protecting the host from *Candida* infection.[14]

Therefore, mechanistically, treatment with IL-17 inhibitors may increase the risk of these infections. However, in our study, there may be a bias for risk evaluation of infections due to the complexity of the condition. As second-line therapy, secukinumab or ixekizumab is recommended over the use of a second TNF-α inhibitor

in patients with primary non-response to the first TNF-α inhibitors according to the ACR/SAA/SPARTN treatment guideline.[15] These patients may have more severe and refractory conditions. Of the included studies on IL-17 inhibitors, 10 (66.7%) studies allowed the patients previously treated with TNF-α inhibitors if they had no adequate response or stopped treatment due to safety or tolerability reasons. Since the detailed information on individuals previously exposed to biologics were not reported, it was difficult to perform further subgroup analysis. In addition, IL-17 inhibitors have been on the market for a relatively short time, and there is less evidence of their adverse events. Therefore, the risk of infections needs to be assessed through more studies and longer follow-up.

Treatment with TNF-α inhibitors showed an increased risk of common infections in patients with axial SpA. However, the results did not suggest a significantly higher risk of serious infections in patients with peripheral SpA and axial SpA treated with TNF-α inhibitors compared with placebo, which was in line with previous studies.[16,17] Among the patients with common infections identified, the majority were minor, especially URTI and nasopharyngitis. With more studies included and consistent results with the

previous meta-analyses, our findings are robust to some extent and it is unlikely that new clinical trials will affect the conclusion of this analysis.

In our study, another important finding was that JAK inhibitors had a significantly increased risk of herpes zoster in patients with peripheral SpA. Patients with some immune-mediated inflammatory diseases intrinsically have an increased risk of herpes zoster infection.[18,19] This risk will further increase in patients treated with JAK inhibitors.[20-22] According to clinical trials and real-world data, patients starting JAK inhibitors or other biologics for rheumatoid arthritis had similar rates of adverse events, including serious infection, but JAK inhibitor initiators had a higher incidence of herpes zoster than other biologics initiators.[20,21] The most characteristic infectious complication with JAK inhibitors is herpes zoster caused by the reactivation of the varicella-zoster virus. The possible mechanism is that the immune response to the varicellazoster virus is partially mediated through the JAK-STAT pathway. In addition, patients with deficiencies in natural killer cell function are susceptible to infection with the varicella-zoster virus. The development and activation of natural killer cells also depend on cytokines mediated through the JAK-STAT pathway. Besides, dose-dependent reductions in peripheral blood natural killer cell counts have been reported for all JAK inhibitors.[23]

There are several study limitations to consider. First, the short period of exposure in the included RCTs is a major solid limitation. Therefore, our results can only represent short-term or medium-term risk assessment of infections using biologics. Second, definitions of infections may differ by individual studies, and many studies did not strictly follow the standard definition of infections within the Medical Dictionary for Regulatory Activities dictionary. These cases were collected based on the original publication case description only with relevant differences between studies. These may result in an increased heterogeneity to a certain extent in collecting these cases. Third, csDMARDs and corticosteroids may further increase the risk of infection. These drugs may introduce the confounding factors in these results. Since the detailed information on individuals previously exposed to these drugs was unavailable to us, it is difficult to perform further sensitivity analysis.

Above all, this meta-analysis showed that biological therapy in patients with SpA may increase the risk of infections, including serious infections, URTI, nasopharyngitis, and *Candida* infection, and JAK inhibitors had an increased risk of herpes zoster in patients with peripheral SpA, which should be paid attention in our clinical practice. These findings have direct implications in the management of many patients treated currently with biologics and a small molecule targeted drugs. Physicians should weigh the benefits and risks of treatments while making decisions. In addition, more studies, with a larger population and longer follow-up and in the real-world setting, will be needed to fully elucidate the safety profile of biologics and small molecule targeted drugs.

Conflicts of interest

None.

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